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Letter to the Editor

Homology between Reaper and the Cell Death Domains of Fas and TNFR1

When engaged by antibodies or by their respective ligands, the cell surface molecules Fas and TNFR1 (the 55 kDa tumor necrosis factor [TNF] receptor) can transduce into cells a signal that often leads to cell death (Armitage, 1994; Nagata and Golstein, 1995). Fas and TNFR1 have homologous extracellular cysteine-rich domains that make them members of the nerve growth factor receptor superfamily. They are also homologous in their cytoplasmic regions for a stretch of 60–70 amino acids, called the death domain, which makes them different from most other members of this superfamily. This dual but dissociated homology, the autonomous death signaling ability of the death domains (Brakebusch et al., 1992; Tartaglia et al., 1993; Itoh and Nagata, 1993; Boldin et al., 1995), and the fact that they are encoded within the last exon of their respective genes (Behrmann et al., 1994) suggest that Fas and TNFR1 may derive from a chimeric ancestor molecule. Such a molecule would have brought together an extracellular region, ancestor to a nerve growth factor receptor domain, and an intracellular cell death signaling module. We reasoned that a derivative of the latter might still exist as an autonomous entity and therefore looked for an intracellular molecule involved in cell death and of about the same size as the death domains.

Reaper, discovered through an elegant genetic approach by White et al. (1994), is a 65 amino acid peptide, the expression of which is both necessary and sufficient for developmental cell death and at least some types of experimental cell death in Drosophila. Mere visual inspection showed homology between reaper and the death domains of TNFR1 and, to a lesser extent, of Fas (Figure 1). This homology was particularly significant because it involves Drosophila and mammalian molecules and because all of these are able to signal cell death. Closer inspection suggested some heterogeneity in the distribution of homologies along reaper. In particular, the middle third of reaper shows the highest density of homologies with TNFR1.

Reaper is involved in a pathway signaling cell death in Drosophila (White et al., 1994). Expression of reaper is both necessary and sufficient to proceed to the next step of this pathway (White et al., 1994). The emergence during evolution of a chimeric molecule covalently linking reaper to an extracellular module would have allowed direct access from the cell exterior to this cell death signaling pathway. For instance, a cell death pathway would thereby have become directly accessible via Fas to cytotoxic T cells bearing the Fas ligand (Rouvier et al., 1993; Suda et al., 1993), allowing the emergence of Fas-based cytotoxicity and immune regulation (Nagata and Golstein, 1995). The Fas and TNFR1 molecules thus turn out to be by and in themselves molecular and conceptual bridges between cell death and cytotoxicity. Also, Fas-based cell death would bypass the initial steps of the cell death signaling cascade, directly reaching the postreaper step. This might account in part for the observations reviewed by Golstein et al. (1991) and Cohen (1991) that death of a given cell induced by cytotoxic T cells is metabolically less demanding than death of the same cell induced by other ways.

It seems likely that soluble cytoplasmic autonomous reaper-like molecules exist in mammalian cells. Search for such molecules could make use of the reported homologies. Interestingly, such hypothetical autonomous molecules are nicely mimicked by constructs using a death domain under an inducible promoter (Boldin et al., 1995). These constructs (and the postulated cytoplasmic homologs to reaper) could cause death when increases in the cytoplasmic concentration of these molecules cause them to aggregate, while Fas and TNFR1 reach the same result by ligand-induced aggregation (Dhein et al., 1992). From another point of view, the possible coexistence of both a reaper homolog and "reaper-including" molecules such as Fas or TNFR1 means that very similar death signaling modules may be reached through distinct pathways, involving either cytoplasmic or direct membrane signaling, thus multiplying for a given module the possibilities of induction and perhaps of regulation. Finally, the observed homologies are in line with conservation throughout evolution of at least some cell death signaling pathways, as already noted for other components of programmed cell death (Vaux et al., 1994).

Figure 1. Amino Acid Sequence Homology between Drosophila Reaper and Part of the Cytoplasmic Domains of Mouse and Human Fas and TNFR1

For Fas and TNFR1, the limits of the sequences listed are those of the death domains as defined by the death-abolishing effect of mutations and deletions (Brakebusch et al., 1992; Tartaglia et al., 1993; Itoh and Nagata, 1993). Alignment of identical residues led to almost exact superimposition of the reaper and death domain sequences. No gap was introduced in the reaper and TNFR1 sequences, and only one gap was introduced in the Fas sequences according to Tartaglia et al. (1993). Residues identical for at least two of the three molecules are boxed, either with lightly stippled boxes if not including reaper or with darkly stippled boxes if including reaper. Searches for homologs of reaper in GenBank using the FASTA program detected none of the other sequences, and, somewhat surprisingly, searches of the death domains of Fas or TNFR1 did not detect reaper. A search of the (QD)XXXX(LT)(AR)E(QAS)(KQ)XXXLXX(WV) motif identified only the reaper, Fas, and TNFR1 sequences. Accession numbers of the sequences used were L31631 for Drosophila *reaper*, M83649 for mouse *Fas* (mFas), M67454 for human *Fas* (hFas), M63121 for mouse *TNFR1* (mTNFR1), and X59238 for human *TNFR1* (hTNFR1).

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